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ORIGINAL REPORT

Risk of Selected Subsequent Carcinomas in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study

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ABSTRACT

Purpose
To determine the risk of subsequent carcinomas other than breast, thyroid, and skin, and to identify factors that influence the risk among survivors of childhood cancer.

Patients and Methods
Subsequent malignant neoplasm history was determined in 13,136 participants (surviving ≥ 5 years postmalignancy, diagnosed from 1970 to 1986 at age < 21 years) of the Childhood Cancer Survivor Study to calculate standardized incidence ratios (SIRs), using Surveillance, Epidemiology, and End Results data.

Results
In 71 individuals, 71 carcinomas were diagnosed at a median age of 27 years and a median elapsed time of 15 years in the genitourinary system (35%), head and neck area (32%), gastrointestinal tract (23%), and other sites (10%). Fifty-nine patients (83%) had received radiotherapy, and 42 (59%) developed a second malignant neoplasm in a previous radiotherapy field. Risk was significantly elevated following all childhood diagnoses except CNS neoplasms, and was highest following neuroblastoma (SIR = 24.2) and soft tissue sarcoma (SIR = 6.2). Survivors of neuroblastoma had a 329-fold increased risk of renal cell carcinomas; survivors of Hodgkin's lymphoma had a 4.5-fold increased risk of gastrointestinal carcinomas. Significantly elevated risk of head and neck carcinoma occurred in survivors of soft tissue sarcoma (SIR = 22.6), neuroblastoma (SIR = 20.9), and leukemia (SIR = 20.9).

Conclusion
Young survivors of childhood cancers are at increased risk of developing subsequent carcinomas typical of later adulthood, underscoring the importance of long-term follow-up and risk-based screening. Follow-up of the cohort is ongoing to determine lifetime risk and delineate individual characteristics that contribute to risk.

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INTRODUCTION

Because the survival rates for childhood cancers have improved to more than 80%, the proportion of childhood cancer survivors within the general population increases every year.[1] Survivors are at risk for multiple late sequelae of therapy, including early mortality.[2-4] Mertens et al,[2] found subsequent malignant neoplasms (SMNs) to be the second most common cause of death, and Robertson et al [5] found them to be the third most common cause of death in survivors.

Factors that might contribute to the risk of an SMN include primary childhood cancer diagnosis, previous therapy received, time from initial diagnosis, and genetic predisposition.[6,7] An increased risk of subsequent leukemia is well-documented after exposure to epipodophyllotoxins and alkylating agents.[8,9] Similarly, the risk of carcinomas of the breast and thyroid, particularly after childhood Hodgkin's lymphoma, has been extensively reported.[10-12]

Carcinomas occurring as an SMN at other sites have been described in survivors of Hodgkin's lymphoma,[10,11,13,14] in aggregate as part of large cohorts of cancer survivors, or for the most common individual cancers.[6,15] These previous studies have suggested that childhood cancer survivors are at risk for carcinomas of the parotid gland,[10,16-19] lung,[11,14,15,20,21] gastrointestinal tract,[11,13,14, 15,20-22] bladder and

kidney,[14,20,23] and female[10,15,24,25] and male genitourinary tract.[10,24,25] Others have described the development of carcinomas after treatment for childhood cancer, without specifying the sites or morphology of these SMNs.[10,11,16-20,22,24,26,27]

With the availability of a large cohort of childhood cancer survivors who have now reached adulthood, we completed a more extensive analysis focused on the risk of carcinoma as an SMN. As SMNs of the breast, thyroid, and skin have already been reported from the Childhood Cancer Survivor Study (CCSS) cohort,[6,28,29] the current report focuses on the risk of carcinomas in all other sites. We also seek to identify patient and treatment characteristics that are associated with an increased risk of developing these carcinomas.

PATIENTS AND METHODS

CCSS Cohort

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional, retrospective cohort of survivors of childhood cancer designed to study the late effects of cancer therapy among 5-year survivors of childhood cancer (funded by the National Institutes of Health and the Children's Cancer Research Fund).[30] Eligibility criteria for participation in the CCSS cohort were: (1) diagnosis of leukemia, CNS tumor, Hodgkin's lymphoma, non-Hodgkin's lymphoma, Wilms' tumor, neuroblastoma, soft tissue sarcoma, or bone tumor; (2) diagnosis and initial treatment at one of the 26 participating oncology centers (see Appendix); (3) diagnosis between January 1, 1970, and December 31, 1986; (4) age younger than 21 years at diagnosis; and (5) survival of ≥ 5 years after diagnosis. Not included were patients with a primary diagnosis of retinoblastoma, non-CNS germ cell tumors, and hepatic tumors.

Baseline data were collected on a wide range of exposures and outcomes, including the development of an SMN, as well as demographic characteristics, smoking and alcohol consumption, and family history. The methodology has been described elsewhere,[30] and copies of study documents are available at www.cancer.umn.edu/ccss. Each participating center's institutional review board reviewed and approved the CCSS protocol and contact documents.

A total of 20,720 patients were identified as eligible for participation in the CCSS. Starting August 1, 1994, 14,372 patients (69%) agreed to participate and completed the baseline questionnaire, 3,017 patients (15%) were lost to follow-up, and 3,189 patients (15%) declined participation. The remaining 142 patients (1%) were undergoing tracing as of November 2002. Complete therapy-related data are available for 13,136 participants who signed a separate consent for medical record abstraction. In 2000, follow-up questionnaires were sent to the 12,046 participants who were alive at baseline, of which 10,388 (86.2%) returned follow-up questionnaires. This analysis thus includes data from both baseline and follow-up questionnaires available as of November 2002.

Cancer Therapy

Detailed therapy-related information was obtained from the medical records of consenting study participants by trained data abstractors using a standardized protocol for all primary cancer therapy (initial treatment, treatment for relapse, and preparative regimen for bone marrow transplantation). History of any chemotherapy (yes/no) was ascertained, as was specific exposure to alkylating agents, epipodophyllotoxins, platinum compounds, and anthracyclines. Radiation exposure was considered as a yes/no variable, and was analyzed for five field sites: head and neck (including brain), chest, abdomen, pelvis, and extremities.

Ascertainment of SMNs

SMNs were ascertained initially through self report from the baseline and follow-up questionnaires. Pathology reports for positive responses were requested from the treating institutions and only pathologically confirmed SMNs by the CCSS Pathology Center (Columbus, OH) were included in the current analysis.

Carcinomas eligible for inclusion in this analysis had the following *International Classification of Diseases of Oncology–2* (ICDO-2) morphology codes with a behavior code of "3" (invasive): 8010 to 8040, epithelial neoplasms not otherwise specified; 8050 to 8080, squamous cell neoplasms; 8120 to 8130, transitional cell papillomas and carcinomas; 8140 to 8380, adenomas and adenocarcinomas; 8430 mucoepidermoid neoplasms; 8440 to 8490, cystic, mucinous, and serous neoplasms; 8550 to 8580, acinar cell and complex epithelial neoplasms; and 9100 to 9109, trophoblastic neoplasms. The included sites were: C00.0 to C14.0, lip, oral cavity, and pharynx; C15.0 to C26.0, digestive organs; C30.0 to C32.0, nasal cavity, sinuses, and larynx; C34.0, lung and bronchus; C51.0 to C58.0, female genital organs; C60.0 to C63.0, male genital organs; C64.0 to C68.0 urinary tract. Excluded were basal cell (8090 to 8110), breast (8500 to 8540) and thyroid neoplasms (8330 to 8350), as well as squamous cell neoplasms (8050 to 8080) occurring in skin sites. Thyroid and breast carcinomas and nonmelanoma skin cancers are of distinct clinical importance, but are included in separate CCSS reports.[28,31]

Statistical Analysis

Cumulative incidence, standardized incidence ratios (SIRs), and absolute excess risk (AER) were used to determine the risk of a carcinoma as an SMN in this cohort, with mortality as a competing risk. Carcinomas occurring within 5 years of the primary diagnosis were excluded since 5 years of follow-up was a criterion for cohort entry. Hence, person-years during the first 5 years after primary diagnosis were not included in calculations. Cumulative incidence was calculated as the percentage of patients who would develop an SMN 5 to 20 years after primary malignancy diagnosis. Age-, sex-, and calendar year–matched SIRs were calculated using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (National Cancer Institute SEER*Stat software version 5.0 [http://seer.cancer.gov/seerstat]). AER was calculated by subtracting the expected number of SMNs in the cohort from the observed number, dividing the difference by person-years of follow-up, and multiplying by 100,000. Because of the small sample size within each tumor morphology and site group, it was not feasible to perform adjusted analyses.

RESULTS

Patient and Carcinoma Characteristics

A total of 677 SMNs were verified in 14,372 CCSS cohort members. Of these, 71 were carcinomas eligible for the current analysis, occurring in 71 patients. All 71 subsequent carcinomas were second malignancies. The median age at diagnosis of the carcinomas was 27 years (range, 10 to 44 years), and the median elapsed time from primary malignancy to was 15 years (range, 6 to 28 years).

Individuals with a subsequent carcinoma were more likely to have the following attributes: older age at diagnosis of their primary neoplasm, primary diagnosis of Hodgkin's lymphoma, soft tissue sarcoma or neuroblastoma, and history of a first-degree relative with cancer (Table 1). Also, cases with a subsequent carcinoma were more likely to have a history of alcohol use (86% *v* 68%; $P = .003$) and a first-degree relative with cancer (32% *v* 13%; $P < .001$), but not tobacco exposure (data not shown).

Table 2 displays the distribution of subsequent carcinoma sites stratified by primary neoplasm. Overall, 25 carcinomas (35%) occurred in the genitourinary system, 23 in the head and neck area (32%), 16 in the gastrointestinal tract (23%), four in the lungs (6%), and three in other sites (4%). Of the 16 gastrointestinal carcinomas, seven were colorectal, five were in the stomach, and the remaining carcinomas were in other intra-abdominal sites. The elapsed time between primary and subsequent carcinoma was longest for patients with primary Wilms' tumor and Hodgkin's lymphoma. Median age at diagnosis of subsequent carcinoma ranged from 22 years for kidney carcinomas to 36 years for lung carcinomas (data not shown).

Table 1. Characteristics of CCSS Participants

Characteristic	Patients With Subsequent Carcinoma* (n = 71)		Rest of Cohort (n = 14,301)		P†
	No.	%	No.	%	
Sex					
Male	32	45.1	7,691	53.8	.14
Female	39	54.9	6,610	46.2	
Age at diagnosis of primary malignancy, years					
< 1	4	5.6	999	7.0	
1-9	24	33.8	7,934	55.5	< .001
10-20	43	60.6	5,368	37.5	
Primary diagnosis					
Leukemia	13	18.3	4,821	33.7	
CNS tumor	4	5.6	1,872	13.1	
HL	18	25.4	1,909	13.4	.004
NHL	6	8.5	1,079	7.5	
Wilms' tumor	3	4.2	1,254	8.8	
NBL	9	12.7	946	6.6	
STS	12	16.9	1,235	8.6	
Bone cancer	6	8.5	1,185	8.3	
Treatment era					
1970-1977	44	62.0	4,795	33.5	< .001
1978-1986	27	38.0	9,506	66.5	
Therapy received for primary malignancy					
Chemotherapy					
Alkylating agents	47	67.1	6,651	53.5	.02
Epipodophyllotoxins	5	7.1	1,213	9.8	.46
Platinum agents	3	4.3	770	6.2	.7
Anthracyclines	27	38.6	5,122	41.3	.53
Radiation therapy	59	84.3	8,427	67.8	.003
Splenectomy	13	18.8	1,456	10.5	.02
Age at subsequent carcinoma, years					
10-19	16	22.5	N/A		N/A
20-29	30	42.3	N/A		
30-39	21	29.6	N/A		
> 40	4	5.6	N/A		
Current vital status					
Alive	50	70.4	12,701	88.8	< .001
Dead	21	29.6	1,600	11.2	

Abbreviations: CCCS, Childhood Cancer Survivor Study, HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NBL, neuroblastoma; STS, soft tissue sarcoma.
*Excluding carcinomas of the breast, thyroid, and skin sites and carcinoma in situ.
†χ^2 test was used to compare the two groups.

Risk Estimates

Overall, the SIR of a subsequent carcinoma was 4.0 (95% CI, 3.1 to 5.1) and was elevated for all primary childhood cancer diagnoses except CNS neoplasms (Tables 2 and 3). Survivors of neuroblastoma (SIR, 24.2; 95% CI, 12.6 to 46.5), soft tissue sarcoma (SIR, 6.2; 95% CI, 3.5 to 11.0), and Wilms' tumor (SIR, 4.8; 95% CI, 1.5 to 14.8) had the greatest risk of developing a subsequent carcinoma. The overall cumulative incidence of developing a subsequent carcinoma of interest was 0.45% at 20 years of follow-up.

Table 3 displays the unadjusted relative risk estimates of subsequent carcinomas stratified by patient and therapy characteristics. Survivors of neuroblastoma had the greatest risk of carcinoma largely because of their elevated risk of developing a kidney tumor (SIR, 329), all of which were renal cell carcinomas. The risk of head and neck carcinomas was elevated in patients with a primary soft tissue sarcoma (SIR, 21.6), leukemia (SIR, 20.9), and neuroblastoma (SIR, 20.9). Survivors of Wilms' tumor had an elevated risk of developing colorectal carcinomas (SIR, 25.4) and other gastrointestinal carcinomas (SIR, 18.0), as did survivors of Hodgkin's lymphoma. Patients with CNS tumors had an elevated risk of developing carcinomas of the head and neck (SIR, 10.1) and kidney (SIR, 11.3), but not of other sites.

Risk estimates varied with other patient characteristics (Table 3). Women had a higher risk of developing carcinomas of the head and neck, kidney, bladder, and some sites in the gastrointestinal tract. For most site categories, patients initially diagnosed at an age younger than 10 years had greater risk. Risk of subsequent carcinoma of the kidney in individuals diagnosed at younger than 1 year old was particularly elevated (SIR, 94.8). Three of four patients in this age category had neuroblastoma.

In terms of therapies (Table 4), patients treated with epipodophyllotoxins had an elevated risk of lung carcinomas (SIR, 73.4 *v* SIR, 1.8 in nonexposed patients), as did patients treated with alkylating

Table 2. Distribution of Subsequent Carcinomas by Primary Neoplasm

Primary Neoplasm	Median Elapsed Time (years)	Site of Subsequent Carcinoma (No.)									
		Head and Neck*	Colon and Rectum	Other GI†	Lung	Female GU‡	Male GU§	Kidney	Bladder	Other‖	Total
Leukemia	12.6	8	0	1	1	0	0	1	2	0	13
CNS	9.3	2	1	0	0	0	0	1	0	0	4
HL	18.7	6	2	4	3	2	0	1	0	0	18
NHL	13.0	2	1	0	0	1	1	0	1	0	6
Wilms' tumor	21.2	0	2	1	0	0	0	0	0	0	3
NBL	15.2	1	0	0	0	3	0	5	0	0	9
STS	13.5	4	0	1	0	3	1	0	2	1	12
Bone tumor	14.3	0	1	2	0	0	0	1	0	2	6
Total	14.7	23	7	9	4	9	2	9	5	3	71

NOTE. Excluding carcinomas of the breast, thyroid, and skin sites, and excluding carcinoma in situ.
Abbreviations: GU, genitourinary; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NBL, neuroblastoma; STS, soft tissue sarcoma.
*Head and Neck includes carcinomas of the tongue (n = 3), gums (n = 1), parotid gland (n = 14), submandibular gland (n = 1), tonsillar fossa (n = 1), hypopharynx (n = 1), nasal cavity (n = 1), and larynx (n = 1).
†Other GI includes carcinomas of the stomach (n = 5), small intestine (n = 1), liver (n = 1), extrahepatic bile duct (n = 1), and pancreas (n = 1).
‡Female GU includes carcinomas of the vulva (n = 1), cervix (n = 2), uterus (n = 3), and ovary (n = 3).
§Male GU includes carcinomas of the prostate (n = 1) and testes (n = 1).
‖Other includes carcinomas of the adrenal glands (n = 1), abdomen not otherwise specified (n = 1), and an unknown site (n = 1).

agents (SIR, 7.0 *v* SIR, 0 in nonexposed). Platinum therapy resulted in significantly elevated SIR estimates for subsequent colorectal (SIR, 14.7) and kidney (SIR, 48.7) carcinomas compared with individuals who had not received this therapy. The specificity of these associations cannot be determined because many of these exposures occurred concurrently in the same patient.

Radiation therapy was associated with an increased risk of all carcinomas except those of the genitourinary tract, and was most marked for carcinomas of the head and neck (SIR, 18.5 *v* 2.3 for cases without radiation therapy). In participants with complete radiation data, the site of the carcinoma had arisen in a previous radiation field for all lung (four of four), 85% head and neck (17 of 20), and 71%

Table 3. Unadjusted SIRs and 95% CIs of Subsequent Carcinomas Stratified by Patient Characteristics

	Site of Subsequent Carcinoma*																	
	H&N		Colon & Rectum		Other GI†		Lung		Female GU		Male GU		Kidney		Bladder		Total	
	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
Overall risk	13.6	8.9 to 20.9	2.7	1.3 to 5.6	5.0	2.6 to 9.7	3.1	1.2 to 8.2	1.3	0.7 to 2.5	3.5	0.9 to 14.0	10.6	5.5 to 20.4	5.1	2.1 to 12.4	4.0	3.1 to 5.1
Sex																		
Male	11.7	6.6 to 20.5	2.8	1.1 to 7.5	1.8	0.5 to 7.4	4.6	1.5 to 14.1	N/A	—	3.5	0.9 to 14.0	8.5	3.2 to 22.6	4.4	1.4 to 13.5	5.1	3.6 to 7.2
Female	14.6	8.1 to 26.3	2.6	0.8 to 7.9	9.9	4.7 to 20.7	1.5	0.2 to 11.0	1.3	0.7 to 2.5	N/A	—	13.3	5.5 to 32.0	7.1	1.8 to 28.5	3.4	2.5 to 4.7
Age at diagnosis of primary neoplasm, years																		
< 1	51.66	12.9 to 206.6	0	0 to 97.5	0	0 to 119.5	0	0 to 253.6	10.06	1.4 to 71.4	0	0 to 259.1	94.8	13.4 to 673.3	0	0 to 229.4	15.7	5.9 to 41.9
1-9	16.2	8.1 to 32.3	5.2	1.7 to 16.3	5.1	1.3 to 20.3	4.8	0.7 to 33.8	1.8	0.6 to 5.4	0	0 to 18.5	29.3	12.2 to 70.5	0	0 to 13.0	5.8	3.9 to 8.6
10-20	10.4	6.0 to 17.9	2.0	0.8 to 5.3	5.1	2.4 to 10.7	2.8	0.9 to 8.6	0.9	0.4 to 2.3	5.0	1.3 to 20.2	4.5	1.5 to 13.9	6.9	2.9 to 16.5	3.2	2.4 to 4.4
Primary neoplasm																		
Leukemia	20.9	10.5 to 41.8	0	0 to 6.0	2.9	0.4 to 20.8	4.7	0.7 to 33.3	0	0 to 1.9	0	0 to 26.4	6.4	0.9 to 45.7	10.6	2.7 to 42.3	3.6	2.1 to 6.2
CNS tumor	10.1	2.5 to 40.3	3.6	0.5 to 25.5	0	0 to 15.7	0	0 to 23.3	0	0 to 4.1	0	0 to 46.9	11.3	1.6 to 80.0	0	0 to 27.8	2.1	0.8 to 5.7
HL	12.3	5.5 to 27.4	2.5	0.6 to 10.1	7.4	2.8 to 19.6	6.6	2.1 to 20.5	0.9	0.2 to 3.8	0	0 to 18.8	3.8	0.5 to 26.7	0	0 to 10.6	3.4	2.1 to 5.4
NHL	11.8	2.9 to 46.0	4.0	0.6 to 28.6	0	0 to 16.9	0	0 to 25.0	2.4	0.3 to 17.1	14.5	2.0 to 102.7	0	0 to 36.6	9.6	1.4 to 68.4	4.1	1.9 to 9.2
Wilms's tumor	0	0 to 40.8	25.4	6.3 to 101.4	18.0	2.5 to 127.6	0	0 to 95.6	0	0 to 10.6	0	0 to 147.4	0	0 to 121.1	0	0 to 97.1	4.8	1.5 to 14.8
NBL	20.9	2.9 to 148.2	0	0 to 63.7	0	0 to 85.5	0	0 to 160.9	19.1	6.2 to 59.1	0	0 to 223.8	329	137 to 791	0	0 to 158.9	24.2	12.6 to 46.5
STS	21.6	8.1 to 57.6	0	0 to 10.7	5.2	0.7 to 37.1	0	0 to 20.6	3.8	1.2 to 11.8	16.62	2.3 to 118.0	0	0 to 32.7	19.8	2.0 to 79.1	6.2	3.5 to 11.0
Bone tumor	0	0 to 12.5	2.7	0.4 to 19.0	7.8	2.0 to 31.2	0	0 to 15.5	0	0 to 3.0	0	0 to 42.4	8.0	1.1 to 56.8	0	0 to 21.9	2.4	1.1 to 5.3
Elapsed time between malignancies, years																		
0-9	17.2	6.5 to 45.9	16.2	5.2 to 50.2	0	0 to 22.2	0	0 to 40.5	0	0 to 4.2	0	0 to 33.1	30.1	7.5 to 120.5	0	0 to 28.1	5.3	2.8 to 10.2
10-19	19.7	12.2 to 31.7	0.8	0.1 to 5.9	5.1	1.9 to 13.5	4.0	1.0 to 15.8	1.9	0.9 to 3.9	4.1	0.6 to 29.3	10.9	4.1 to 29.1	4.3	1.1 to 17.3	4.8	3.5 to 6.5
≥ 20	2.9	0.7 to 11.6	2.5	0.8 to 7.7	5.8	2.4 to 13.8	2.8	0.7 to 11.0	0.8	0.2 to 3.1	4.2	0.6 to 30.0	7.2	2.3 to 22.3	7.5	2.4 to 23.3	2.8	1.8 to 4.3

Abbreviations: SIR, standardized incidence ratio; H&N, head and neck; GU, genitourinary; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; STS, soft tissue sarcoma; NA, not available.
*Excluding carcinomas of the breast, thyroid, and skin sites, and excluding carcinoma in situ.
†Other GI refers to gastrointestinal sites excluding colon and rectum.

Table 4. Unadjusted SIRs and 95% CIs of Subsequent Carcinomas Stratified by Treatment Characteristics

	Site of Subsequent Carcinoma*																	
	H&N		Colon & Rectum		Other GI†		Lung		Female GU		Male GU		Kidney		Bladder		Total	
	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI	SIR	95% CI
Treatment Era																		
1970-1977	9.0	4.9 to 16.7	2.4	0.9 to 6.3	6.8	3.4 to 13.5	2.1	0.5 to 8.5	1.4	0.6 to 3.1	5.4	1.3 to 21.5	7.0	2.6 to 18.6	7.8	3.3 to 18.7	3.9	2.9 to 5.2
1978-1986	19.3	11.2 to 33.2	3.3	1.1 to 10.3	1.7	0.2 to 11.7	5.6	1.4 to 22.3	1.1	0.4 to 3.5	0	0 to 15.2	18.1	7.5 to 43.4	0	0 to 9.1	4.3	2.9 to 6.2
Treatment type																		
Chemotherapy																		
Yes	17.1	10.9 to 26.8	3.8	1.7 to 8.4	7.4	3.7 to 14.8	5.3	2.0 to 14.1	1.1	0.5 to 2.7	5.9	1.5 to 23.6	13.7	6.5 to 28.7	8.5	3.5 to 20.3	5.4	4.2 to 6.9
No	6.4	2.1 to 20.0	1.4	0.2 to 9.8	2.0	0.3 to 14.1	0	0 to 7.3	2.1	0.8 to 5.7	0	0 to 18.9	8.2	2.1 to 32.8	0	0 to 11.4	2.3	1.3 to 4.1
Alkylating agents																		
Yes	21.3	13.2 to 34.2	3.4	1.3 to 9.1	8.7	4.2 to 18.3	7.0	2.6 to 18.7	0.9	0.3 to 2.9	0	0 to 11.9	13.2	5.5 to 31.6	9.2	3.4 to 24.4	5.9	4.4 to 7.9
No	6.4	2.7 to 15.5	2.6	0.8 to 8.2	2.5	0.6 to 10.2	0	0 to 5.0	1.9	0.8 to 4.2	8.2	2.0 to 32.7	10.7	4.0 to 28.4	2.4	0.3 to 17.0	2.9	1.9 to 4.4
Epipodophyllotoxin																		
Yes	34.9	8.7 to 139.7	0	0 to 42.5	0	0 to 62.7	73.4	18.4 to 293.6	4.8	0.7 to 34.4	0	0 to 163.0	0	0 to 139.8	0	0 to 112.5	10.0	4.2 to 24.1
No	13.2	8.5 to 20.4	3.1	1.5 to 6.6	5.8	3.0 to 11.2	1.8	0.4 to 7.0	1.3	0.6 to 2.6	4.2	1.0 to 16.7	12.3	6.4 to 23.6	6.0	2.5 to 14.5	4.2	3.3 to 5.4
Platinum agents																		
Yes	0	0 to 61.7	14.7	2.1 to 104.1	0	0 to 66.1	0	0 to 112.3	5.3	0.8 to 37.7	0	0 to 207.9	48.7	6.9 to 345.7	0	0 to 119.2	6.5	2.1 to 20.3
No	14.4	9.5 to 21.9	2.7	1.2 to 6.0	5.8	3.0 to 11.2	3.5	1.3 to 9.4	1.3	0.7 to 2.6	4.1	1.0 to 16.6	10.89	5.5 to 21.8	6.0	2.5 to 14.5	4.4	3.4 to 5.5
Anthracyclines																		
Yes	23.5	13.3 to 41.3	2.8	0.7 to 11.0	4.1	1.0 to 16.2	6.1	1.5 to 24.3	1.0	0.2 to 3.9	6.6	0.9 to 47.1	12.9	4.2 to 40.0	3.7	0.5 to 26.2	5.4	3.7 to 7.9
No	9.4	5.1 to 17.5	3.2	1.3 to 7.6	6.4	3.0 to 13.4	2.4	0.6 to 9.6	1.6	0.7 to 3.4	2.9	0.4 to 20.5	11.5	5.2 to 25.6	6.9	2.6 to 18.3	4.0	2.9 to 5.4
Splenectomy																		
Yes	12.8	5.3 to 30.8	1.6	0.2 to 11.4	6.9	2.2 to 21.3	2.7	0.4 to 19.4	1.2	0.3 to 4.9	0	0 to 22.6	4.7	0.7 to 33.3	0	0 to 13.2	3.1	1.8 to 5.3
No	12.9	8.0 to 20.8	3.2	1.5 to 7.2	4.7	2.1 to 10.5	3.4	1.1 to 10.6	1.4	0.7 to 2.9	4.8	1.2 to 19.4	10.1	4.5 to 22.4	7.2	3.0 to 17.2	4.3	3.3 to 5.6
Radiation																		
Yes	18.5	12.1 to 28.4	3.6	1.6 to 7.9	7.0	3.5 to 13.9	4.7	1.8 to 12.5	1.1	0.5 to 2.6	2.8	0.4 to 19.9	12.8	6.1 to 26.9	6.4	2.4 to 17.2	5.1	4.0 to 6.6
No	2.3	0.3 to 16.0	1.6	0.2 to 11.2	2.3	0.3 to 16.1	0	0 to 9.4	2.3	0.9 to 6.1	7.2	1.0 to 51.0	9.5	2.4 to 38.0	4.3	0.6 to 30.4	2.5	1.4 to 4.6

Abbreviations: SIR, standardized incidence ratio; H&N, head and neck; GU, genitourinary.
*Excluding carcinomas of the breast, thyroid, and skin sites, and excluding carcinoma in situ.
†Other GI refers to gastrointestinal sites excluding colon and rectum.

gastrointestinal tract carcinomas (10 of 14; not shown). Only 25% of the renal cell carcinomas (two of eight) and 20% of the bladder carcinomas (one of five) arose within a region of previous radiation.

Of the 23 subsequent head and neck carcinomas, 14 had developed in the parotid gland (61%) following a variety of primary neoplasms, including leukemia (seven), CNS tumor (one), Hodgkin's lymphoma (four), non-Hodgkin's lymphoma (one), and soft tissue sarcoma (one; data not shown). Seventy-eight percent of the parotid tumors (11 of 14) occurred at a site of previous radiation exposure and 71% were of mucoepidermoid morphology (10 of 14). Among the seven patients with a primary diagnosis of leukemia, five had cranial radiation, one had not received radiation, and one had radiation of an unknown site.

Patients Without Radiation Exposure to Carcinoma Site

Table 5 displays the treatment history of the 22 (33%) of the 71 cases with carcinomas in a region not previously directly exposed to radiotherapy; 50% (11 of 22) were in patients without any radiation exposure and 50% (11 of 22) received radiation to a distant site. Sixteen (73%) of the 22 patients without direct radiation to the carcinoma had received alkylating agents. Four individuals who developed an SMN had received neither chemotherapy nor radiation therapy. Two had neuroblastoma with a subsequent ovarian carcinoma, one had soft tissue sarcoma with a subsequent carcinoma of the cervix, and one had CNS tumor with a subsequent renal cell carcinoma. This last patient reported a father with liver carcinoma at 31 years old.

DISCUSSION

The Childhood Cancer Survivor Study comprises the largest and most extensively studied cohort of individuals established to date for the study of late effects of cancer and its treatment in children. To our knowledge, this report is the first in the literature that focuses specifically on the risk of certain adult-type carcinomas in childhood cancer survivors, as well as on patient and treatment characteristics that may alter this risk. Previous CCSS reports have focused on the development of second malignancies in general,[6] breast cancer,[28] thyroid cancer,[31] and nonmelanoma skin cancer.[29]

Among 5-year survivors of childhood cancers treated between 1970 and 1986, we found a four-fold increased risk of adult-type carcinomas (excluding carcinomas of the breast, thyroid, and skin) occurring at earlier ages than is typically seen. This is in comparison with the risk of subsequent breast cancer (24.7; 95% CI, 19.3 to 31.0) and thyroid carcinoma (11.3; 95% CI, 8.2 to 15.3) found by others in the CCSS cohort. The incidence of the majority of these carcinomas in the general population begins to rise from ages 41 to 50 years, and reaches its peak from ages 50 to 70 years.[1] Development of these carcinomas is unusual at younger than 40 years, yet are occurring at a median age of 27 years in our sample, and at a four-fold increased rate relative to the SEER population. Some of the most compelling associations found were the elevated risks of renal cell carcinoma among patients with neuroblastoma; gastrointestinal carcinomas among patients with Wilms' tumor and Hodgkin's lymphoma; and head and neck carcinomas among patients with leukemia, neuroblastoma, and

Table 5. Subsequent Carcinomas in Patients Without Previous Radiation Exposure to Carcinoma Site

Primary Neoplasm*	Sex	Age at Primary Neoplasm (years)	Treatment Era*	Age at Carcinoma Diagnosis (years)	Chemotherapy	Radiation Site	Carcinoma Site	Carcinoma Morphology†
1. Leukemia	f	15.3	E	30.0	Asp, MP, MTX, PDN, V	—†	Bladder	TCC
2. CNS tumor	f	17.6	E	23.9	—†	—†	Kidney	RCC
3. CNS tumor	f	12.2	E	19.3	AC, Asp, C, CCNU, DN, HU, MTX, PDN, TG, V	Chest	Rectum	ADE
4. HL	f	15.8	E	38.6	H, P, PDN, V	Chest, Neck	Pancreas	ADE
5. NHL	m	11.0	E	25.8	MP, MTX, PDN, V	—†	Testis	TBN
6. NHL	m	13.2	E	39.7	C, MP, MTX, PDN, V	Brain, Chest, Neck	Bladder	SCC
7. NBL	f	0.1	L	10.2	C, D	—†	Submandibular gland	MEN
8. NBL	f	6.6	E	17.2	—†	—†	Ovary	SCA
9. NBL	f	4.9	L	19.2	—†	—†	Ovary	SCA
10. NBL	m	2.8	L	19.7	C, D, DTIC, V	Head, Neck	Kidney	RCC
11. NBL	m	1.2	L	16.5	C, DTIC, V	Neck	Kidney	RCC
12. NBL	f	1.0	L	9.9	C, DTIC, M	Head	Kidney	RCC
13. STS	f	15.5	E	27.0	MTX	—†	Uterus	TBN
14. STS	f	15.9	E	28.3	—†	—†	Cervix	SCC
15. STS	f	15.2	L	26.2	AD, B, BCNU, C, CDDP, D, DX, MTX, PDN, V	Limb	Larynx	SCC
16. STS	m	13.9	L	26.0	AD, C, D, DTIC, V	Abdomen	Parotid	MEN
17. STS	m	18.9	E	43.0	AD, C, D, DTIC, V	Limb	Bladder	TCC
19. STS	m	10.3	E	36.2	AD, C, V	Limb	Bladder	TCC
18. STS	m	7.2	E	20.6	AD, C, V	Head	Adrenal	ADE
20. Bone tumor	m	16.8	E	34.8	C, V	—†	Stomach	EPI
21. Bone tumor	m	15.7	L	22.8	AD, B, C, CB, CDDP, D, FU, I, IF, MTX, VP	—†	Colon	MAC
22. Bone tumor	f	11.4	L	25.3	CDDP, D	—†	Kidney	RCC

Abbreviations: HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; NBL, neuroblastoma; STS, soft tissue sarcoma; f, female; m, male; E, early; L, late; AC, cytarabine; AD, actinomycin; Asp, asparaginase; B, bleomycin; BCNU, 1,3-bis(2-chloroethyl)−1-nitrosurea; C, cyclophosphamide; CB, carboplatin; CCNU, 1-(2-chloroethyl)−3-cyclohexyl-1-nitrosurea; CDDP, cisplatinum; D, Doxorubicin; DN, daunorubicin; DTIC, dacarbazine; DX, dexamethasone; FU, 5-fluorouracil; H, nitrogen mustard; HU, hydroxyurea; I, Ifosfamide; IF, interferon; M, melphalan; MP, 6-mercaptopurine; MTX, methotrexate; P, procarbazine; PDN, prednisone; TG, 6-thioguanine; V, vincristine; VP, etoposide; ADE, adenocarcinoma; EPI, epithelial neoplasm; MAC, mucinous adenocarcinoma; MEN, mucoepidermoid neoplasm; RCC, renal cell carcinoma; SCA, serous cystadenoma; SCC, squamous cell carcinoma; TBN, trophoblastic neoplasm; TCC, transitional cell carcinoma.
*Treatment era divided into early (early: 1970-1977) and late (late: 1978-1986).
†No therapy of this type was given.

soft tissue sarcoma. The median elapsed time between the diagnosis of the primary neoplasm and of the carcinoma was relatively long at 15 years, emphasizing the need for long-term monitoring of adult survivors of childhood malignancies for complications related to their previous disease and therapy.

Renal cell carcinoma was the most common SMN diagnosed in neuroblastoma survivors in this cohort. Others have also reported a possible association between renal cell carcinoma and neuroblastoma[23,32-36] but the pathophysiology remains poorly understood. In 2005, Altinok et al[23] reported 21 previously published cases of renal cell carcinoma occurring after neuroblastoma; one of those patients also had sickle cell disease. Previous authors[35] have suggested that exposure to cyclophosphamide may play a role in the development of renal cell carcinoma. In the present study, only two of the five renal cell carcinomas following neuroblastoma arose within the radiation field, and four of the five patients received cyclophosphamide.

Our study concluded that there is a 4.5-fold increased risk of gastrointestinal carcinomas and a 6.6-fold increased risk of lung carcinomas in survivors of Hodgkin's lymphoma, consistent with previous reports.[13,14,21] In unadjusted analyses, gastrointestinal carcinomas were associated with radiation and alkylator therapy. Combined radiotherapy and alkylator therapy has been reported to significantly increase the risk of stomach and colon cancers in Hodgkin's lymphoma survivors,[13,14] but this potential interaction could not be tested in our study because of small sample sizes. Our data suggest that survivors of primary Wilms' tumors have a 22-fold increased risk of gastrointestinal carcinomas, a finding that has not been previously reported. These results are compelling, but must be viewed with caution because of our small sample size.

SMNs of the head and neck are the most frequent site of carcinomas in our sample, largely due to parotid gland carcinomas of mucoepidermoid morphology. Ninety percent of these carcinomas followed head and neck radiation. In leukemia survivors with complete radiation data, all parotid carcinomas occurred following cranial radiation. Radiation exposure is a known risk factor for the development of salivary gland tumors.[37,38] Several studies have shown an increased risk of salivary gland tumors following radiation for both benign and malignant conditions in children.[13,39-41]

Radiation is a well-known risk factor for the development of SMNs,[6,42] with some of the most compelling evidence in survivors of Hodgkin's lymphoma following mantle radiation.[10-12] In our sample, radiation therapy was associated with an increased risk of all carcinomas except those of the reproductive organs, and was most strongly associated with the development of head and neck carcinomas. The

majority of the carcinomas reported in our cohort arose within a radiation-exposed site, but one third of the carcinomas occurred in individuals without radiation exposure or in patients who received radiation to a site distant to that of the carcinoma. Furthermore, there were four individuals who developed an SMN who had no chemotherapy or radiotherapy and no known family history of cancer. The collection of buccal cell samples for molecular genetics analysis and the collection of more extensive family history data from CCSS cases is ongoing in the CCSS in order to explore the association between genetic predisposition to cancer and the risk of SMNs.

Limitations to our study should be addressed. Eligibility for entry onto the CCSS cohort was limited to 5-year survivors, excluding individuals who either died or developed an SMN before the 5-year eligibility. Underascertainment of SMNs may have occurred if an SMN developed after the initial contact but was not reported because of a loss to follow-up or because the participant died and the respondent to the questionnaire was unaware of the malignancy. However, National Death Index searches are done with regular frequency on recently deceased CCSS cases, and the cause of death is ascertained. In addition, this analysis evaluated a heterogeneous group of survivors with varied carcinomas and different therapies, which may not be representative of currently treated patients. Efforts are currently underway to update the cohort with patients treated more recently. Finally, although this represents the largest group of secondary carcinomas reported to date, the sample size remains too small to perform adjusted analyses to determine the independent contribution of treatment and patient factors.

This report underscores the importance of continued long-term monitoring for subsequent adult-type carcinomas in survivors of pediatric malignancies well into adulthood. Some of the strongest associations were between primary neuroblastoma and renal cell carcinomas, primary leukemia and parotid gland carcinomas, and primary Wilms' tumor and gastrointestinal carcinomas. As has previously been emphasized for survivors of Hodgkin's lymphoma,[21] our findings support risk-based monitoring for all childhood cancer survivors based on their disease and exposure history, as outlined by the Children's Oncology Group (http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf). Ongoing efforts to reduce the carcinogenicity of current therapies should continue, particularly limiting radiation exposure whenever possible to do so without compromising survival. As the CCSS cohort continues to age, follow-up analyses will be conducted to further define the lifetime risk of subsequent carcinomas in survivors of childhood cancer, and to better delineate individual characteristics that may modify this risk.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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